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November 15, 2006

Mr. Charles M. Auer, Director
Office of Pollution Prevention and Toxics (7401M)
Ariel Rios Building
USEPA Headquarters
1200 Pennsylvania Ave., N.W.
Washington, D. C. 20460

Attn: Chemical Right-to-Know Program

RE: HPV Chemical Challenge Program, AR-201-14947

Dear Mr. Auer:

Thank you for your letter dated September 29, 2006, which mentioned a response about a final data package submission for Glyphosate Intermediate (GI) (CAS RN: 5994-61-6) relative to the High Production Volume (HPV) Challenge Program. The letter noted that EPA had commented on the robust summaries and test plan submission, but Monsanto Company had not yet responded.

Monsanto considers the submitted test plan and robust summaries for GI to be the final data package for the purposes of the HPV Challenge Program. Since modifications to the submission were considered to not be necessary, it seemed that a response was not needed in order to finalize the submission.

~~Monsanto is impressed with the thorough review and detailed comments provided by EPA.~~ EPA noted that the submitted data for most endpoints were adequate for the purposes of the HPV program, reserving judgment in a few instances such as a gene mutation endpoint where additional information for the robust summaries was requested. Monsanto also received comments from People for the Ethical Treatment of Animals (PETA) and Environmental Defense. PETA commented on the good example of using data from related compounds, as requested by EPA, and particularly noted, "With considerable similarity between GI and glyphosate in chemical structure, chemical properties and chemical degradation products, the similar conclusion about GI not posing unreasonable risks to human health or the environment can be reached."

Summaries of human risk assessment and safety evaluation, ecotoxicological risk assessment, toxicology studies, and environmental fate studies for glyphosate are all provided in the appendix attached to the robust summaries for GI. Perhaps EPA did not consider the data provided in the appendix in addition to and in support of the robust summaries of studies conducted on GI itself. Since GI is only produced and used at very few manufacturing sites, and converted entirely into glyphosate before any significant environmental exposures can occur, the overall objectives of the HPV Challenge Program are certainly benefited by including this additional information.

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To briefly respond to the specific comments provided by EPA, Monsanto wishes to add the following information:

1. Physicochemical Properties. EPA commented that melting point, vapor pressure, partition coefficient and water solubility endpoints are adequate. EPA commented that information besides "not distillable" needed to be added to the boiling point robust summary. Since it is clear from the melting point robust summary that GI decomposes upon heating above 200 °C, this is adequate as is. Unfortunately, a reference cited for physical-chemical data was given with an incorrect Monsanto Company report number. Instead of MSL-7663 (1985), the correct report number is MSL-5136 (1985).

2. Environmental Fate. EPA commented that photodegradation and stability in water endpoints are adequate, while biodegradation used acclimated rather than un-acclimated cultures, and fugacity modeling data were needed to assess the distribution of GI in the environment. Similar to glyphosate, GI is a non-volatile material and is not expected in the vapor phase in significant amount to allow atmospheric oxidation. The robust summary for GI pertained to the manufacturing waste stream environment that is actually encountered. The appendix provided a summary of environmental fate studies of glyphosate including a summary of numerous studies showing that glyphosate is degraded by un-acclimated soil microorganisms in numerous soils and geographies. Also, because actual studies such as the adsorption/desorption data provided in the robust summaries and appendix already demonstrate extensive binding to soils, combined with actual studies on leaching and runoff and volatility, modeling data will not provide any additional useful information about how GI would be distributed in the environment.

3. Health Effects. EPA commented that acute, repeated-dose, reproductive and developmental toxicity endpoints are adequate, while reserving judgment on the genetic toxicity endpoint pending additional information and asking for data for the chromosomal aberration endpoint.

   For the repeated-dose summary, although adequate, EPA commented that the summary lacked a list of microscopically examined organs and tissues, characterization of dermal lesions, and information concerning evaluation of blood parameters. A detailed list of examined organs and tissues and blood parameters goes beyond the scope of a study summary; and all positive, treatment-related findings were already included in the robust summary. A detailed list where no additional findings are present would not enhance the summary. Similarly, for the reproductive summary, although adequate, EPA requested additional information regarding particle size, microscopically examined female reproductive organs, incidence of effects and statistical methods and significance. Again, all the significant or treatment-related effects were already included in the robust summary and the additional information would go beyond the scope of a study summary.

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For the Ames test, EPA commented that tested concentrations ranged from 0.1 to 500 µg/plate with no evidence of cytotoxicity at the highest concentration and no justification was given for the selection of these concentrations. GI was tested over a series of concentrations. Unfortunately GI turns the culture media acidic at concentrations of 500 µg/mL and above, resulting in qualitative or quantitative chemically induced physiological effects at the higher dose levels. Therefore the concentration range of 0.1 to 500 ug/plate was selected. Positive and negative control assays were conducted with each experiment. The negative control was DMSO, and a number of positive controls were used in the activation (methylnitrosoguanidine, 2-nitrofluorene and quinacrine mustard) and non-activation (2-anthramine, 2-acetylaminofluorene and 8-aminoquinoloine) assays. Positive control responses were 9 times or greater than the controls. Because the procedures used to evaluate the mutagenicity of the chemical were semiquantitative, the criteria used to determine a positive effect were inherently subjective and were based primarily on a historical control data base. The criteria for a positive response were as follows:

Strains TA-1535, TA-1537 and TA-1538	If the solvent control value is in the normal range, a chemical that produces a positive dose response over three concentrations with the lowest increase equal to twice the solvent control value is considered to be mutagenic.
Strains TA-98, TA-100 and D4	If the solvent control value is within the normal range, a chemical that produces a positive dose response over three concentrations, with the highest increase equal to twice the solvent control value for TA-100 and two to three times the solvent control value for strains TA-98 and D4, is considered to be mutagenic. For these strains, the dose response increase should start at approximately the solvent control value.
Pattern	Because TA-1535 and TA-100 were both derived from the same parental strain (G-46) and because TA-1538 and TA-98 were both derived from the same parent strain (D3052), there is a built-in redundancy in the microbial assay. In general, the two strains of a set respond to the same mutagen and such a pattern in sought. It is also anticipated that if a given strain responds to a mutagen in non-activation tests it will generally do so in activation tests. (The converse of this is not expected.) While similar response patterns are not required for all mutagens, they can be used to enhance the reliability of an evaluation decision.
Reproducibility	If a chemical produces a response in a single test that cannot be reproduced in one or more additional runs, the initial positive test data loses significance.

No statistical methods were used.

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For genetic toxicity data for chromosomal aberrations, the closest structural analog to GI is glyphosate. During a final step in the well-controlled and carefully engineered manufacturing process of the glyphosate technical material, GI is converted to glyphosate by removal of a single N-carboxymethyl moiety. Glyphosate has been extensively evaluated for all toxicological endpoints including genetic toxicity. An extensive review of the genetic toxicology studies with glyphosate can be found in the Williams et al., 2000 publication (pages 131-141) in the Appendix. No evidence of genotoxic activity was observed in standard assays conducted according to international guidelines, including *in vitro* and *in vivo* chromosome aberration studies.

For developmental toxicity, the study guideline was Section 83-3 of the EPA Guidelines; Subdivision F for Hazard Evaluation, Human and Domestic Animals, issued November, 1982. All statistical analyses compared the treatment groups to the control groups with the level of significance of $p<0.05$ and $p<0.01$. All means were accompanied by standard deviations. The statistical methods were as follows:

- Chi-square test criterion with Yate's correction for 2x2 contingency tables and/or Fisher's exact probability test as described by Siegel to judge for significance of difference for male to female sex distribution and the number of litters with malformations.
- Mann-Whitney U-test as described by Siegel and Weil to judge significance of difference for the number of early and late resorptions and postimplantation loss.
- Analysis of variance (one-way classification), Bartlett's test for homogeneity of variances and the appropriate t-test (for equal or unequal variances) as described by Steel and Torrie using Dunnett's multiple comparison tables to judge significance of differences for the mean number of viable fetuses, total implantations, corpora lutea and mean fetal body weights.

Maternal toxicity was only observed at the high-dose of 400 mg/kg/day and included mortality (6/25) and decreased food consumption and body weight.

4. Ecological Effects. EPA commented that submitted data are adequate for all endpoints.

The HPV registration number for Monsanto Company is

Sincerely,

Clyde L. Livingston
Chemical Regulatory Compliance
Monsanto Company